A New Tox21 Strategic and Operational Plan

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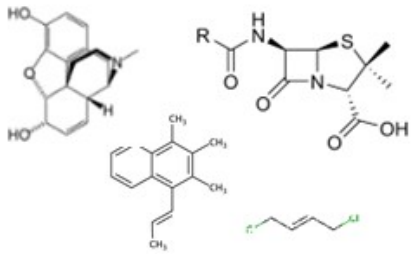
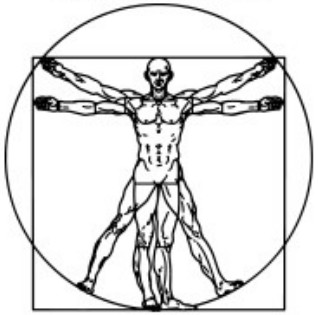
EPA NIH National Institute of Environmental Health Sciences NIH National Center for Advancing Translational Sciences FDA NTP National Toxicology Program U.S. Department of Health and Human Services

Underlying Issues Facing Toxicology

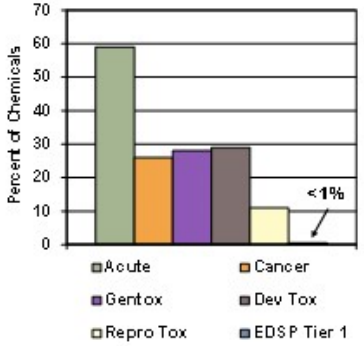
Number of Chemicals /Combinations to Test



Human Relevance of Existing Tests



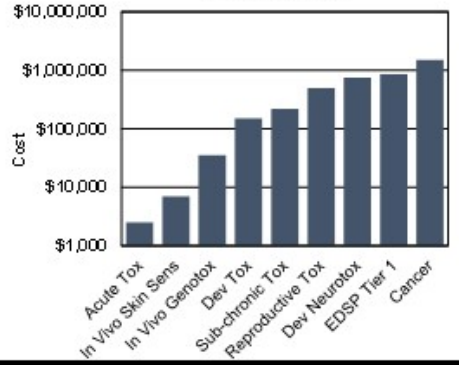
Lack of Data for Environmental Chemicals



Modified from Judson *et al.*, EHP 2010

Ethics Concerns

Economics



Formation and Renewal of U.S. Tox21 Federal Partnership

MEMORANDUM OF UNDERSTANDING

ON

High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

MOU Signed February, 2008; Revised July, 2010

XI. APPROVAL

National Toxicology Program

Linda S. Birnbaum, Ph.D., DABT, ATS — Date: 5-11-15
Director
National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Advancing Translational Sciences

Christopher P. Austin, M.D. — Date: 5/20/2015
Director
National Center for Advancing Translational Sciences
National Institutes of Health

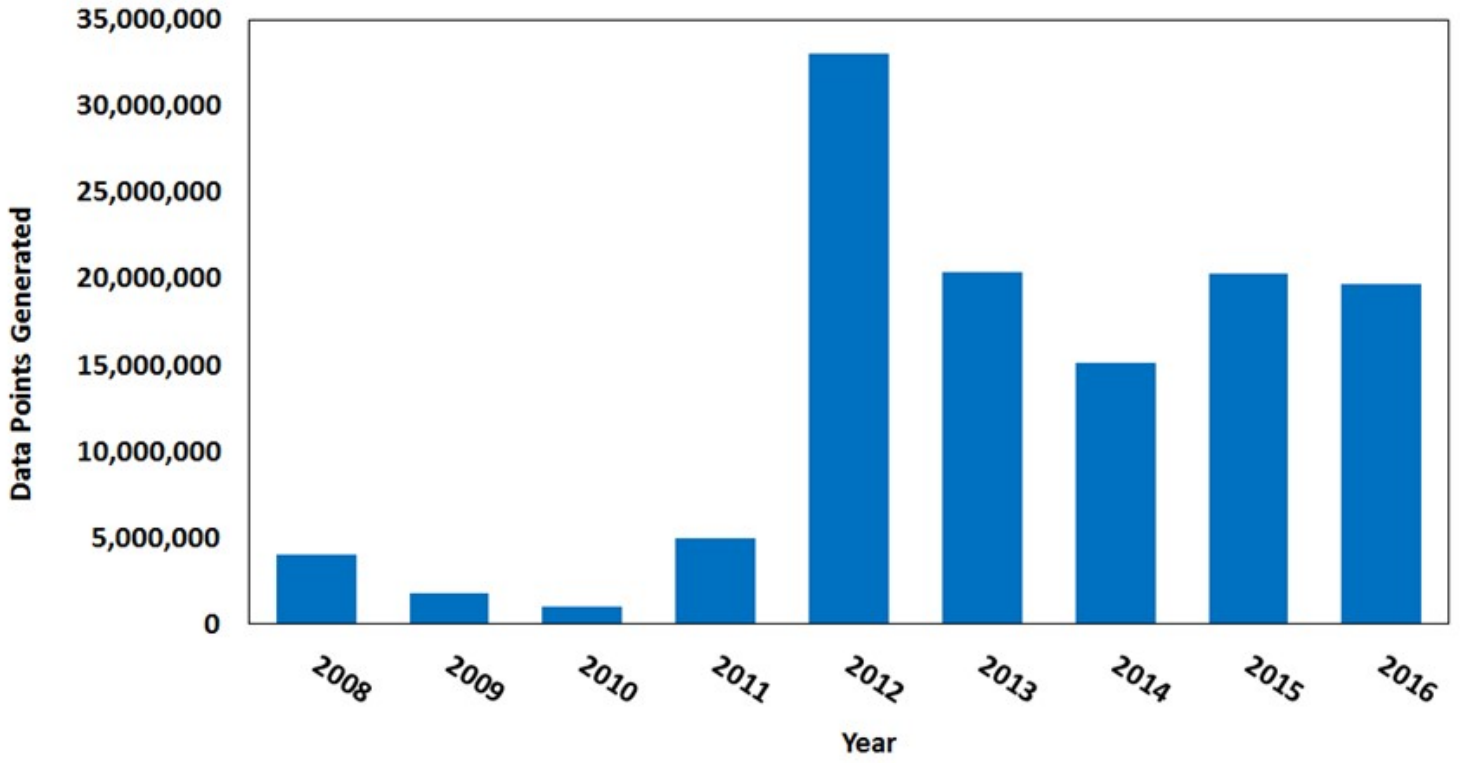
U.S. Environmental Protection Agency

Lek G. Kadeli — Date: 6/16/15
Acting Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency

U.S. Food and Drug Administration

Susan T. Mayne, Ph.D. — Date: 5/27/15
Director
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration

Toxicity Testing Data Generated by Tox21



*Total number of assays is ~70

Scientific, Public, and Regulatory Impact of Tox21

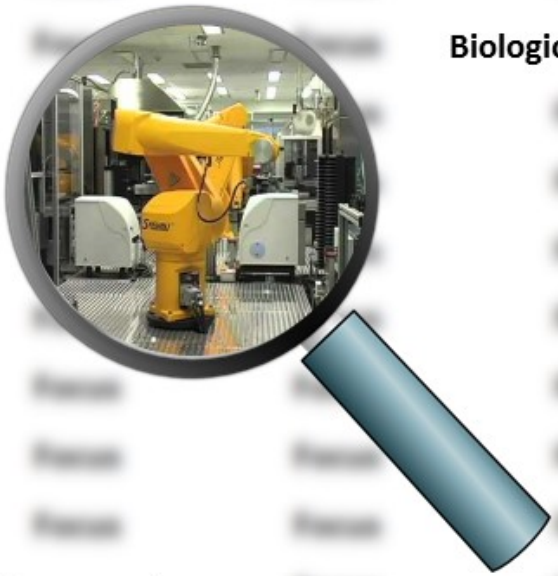
- Tox21 collaboration has published over 200 scientific peer-reviewed articles in over 56 journals
- Top 5 Tox21 publications cited an average of over 100 times (Web of Science)
- Tox21 mentioned in over 70 news articles, 13 blogs, 461 Twitter posts, and 8 Wikipedia articles (AltMetric, Aug, 2017)
- Tox21 publications cited in over 140 policy-related and expert panel documents (AltMetric, Aug, 2017).
  - National Academies of Science Reports (~80)
  - Publications Office of the European Union (~15)
  - European Food Safety Authority (~5)
  - World Health Organization (~5)

But, the Focus of Tox21 has been Predominantly on HTS

Need to Expand Vision to Move Toxicity Testing into 21st Century

Validation

Biokinetics

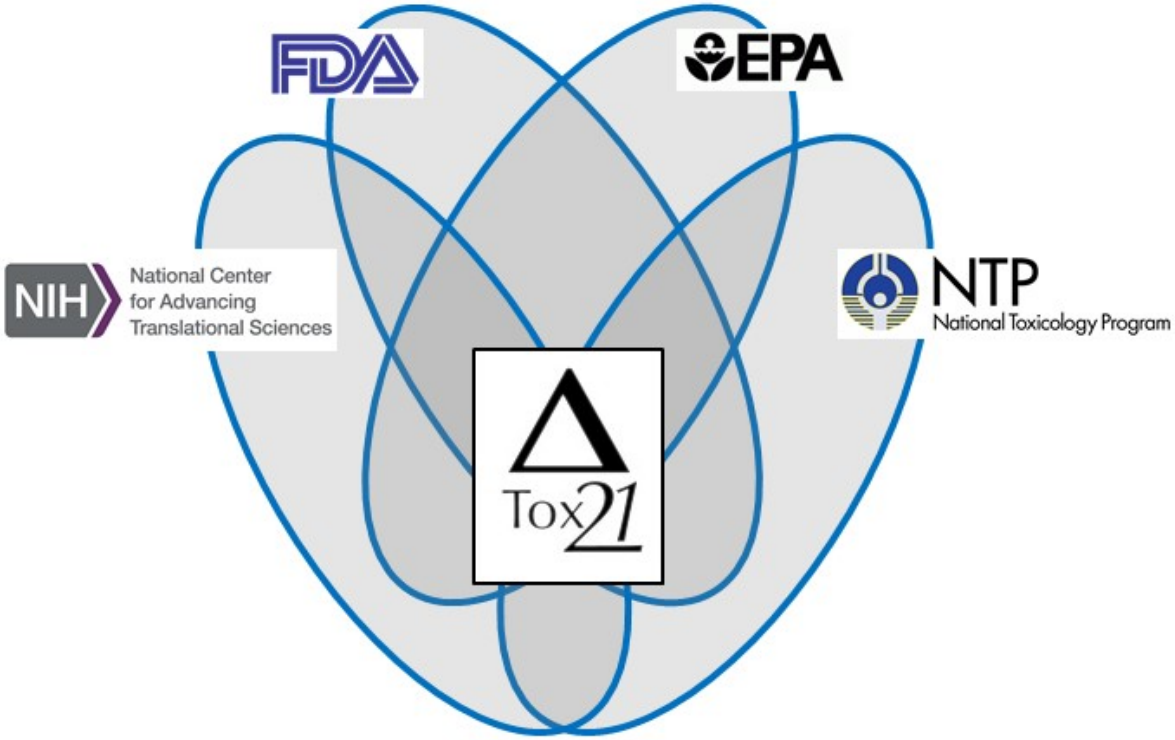


Organotypic Assays

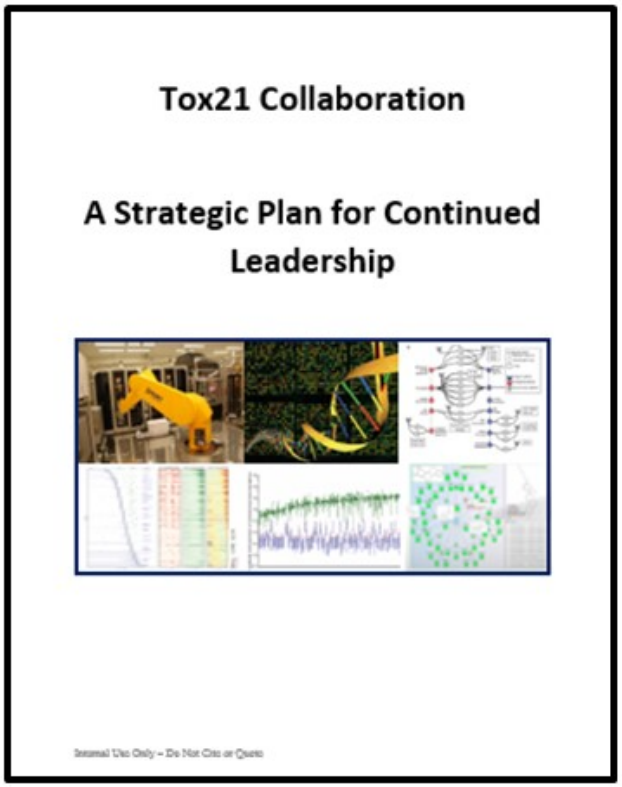
Biological Coverage

Metabolic Competence

The Challenge



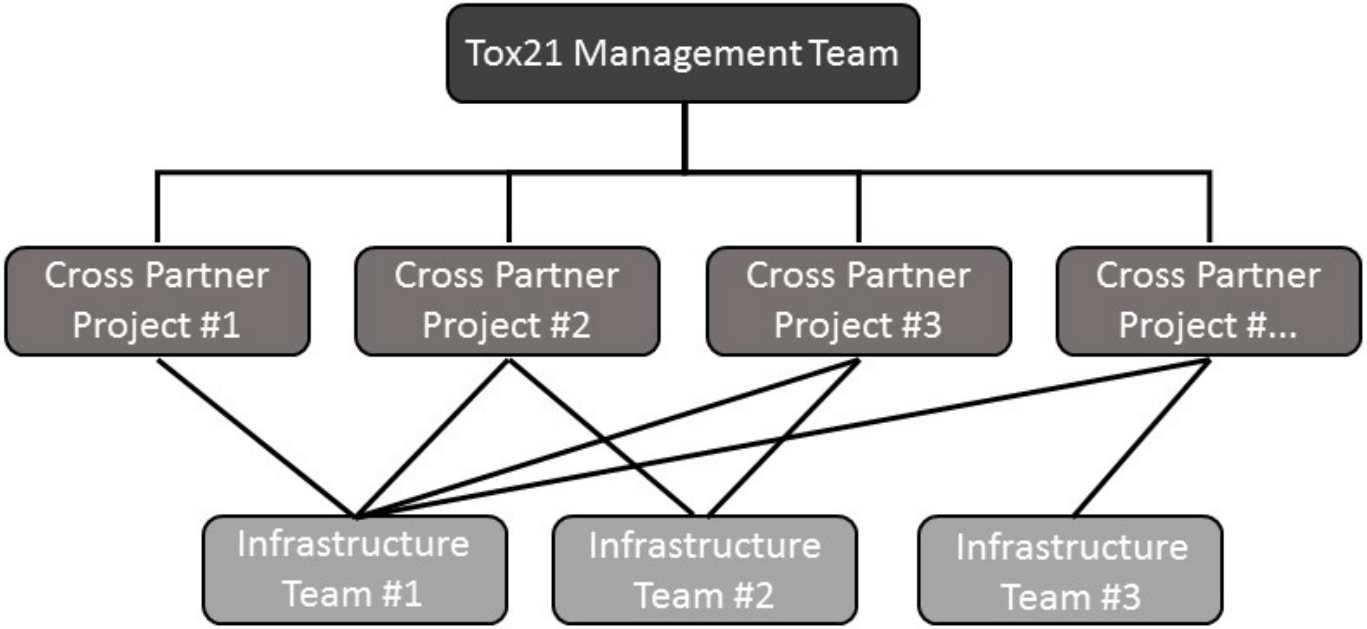
New Tox21 Strategic and Operational Plan



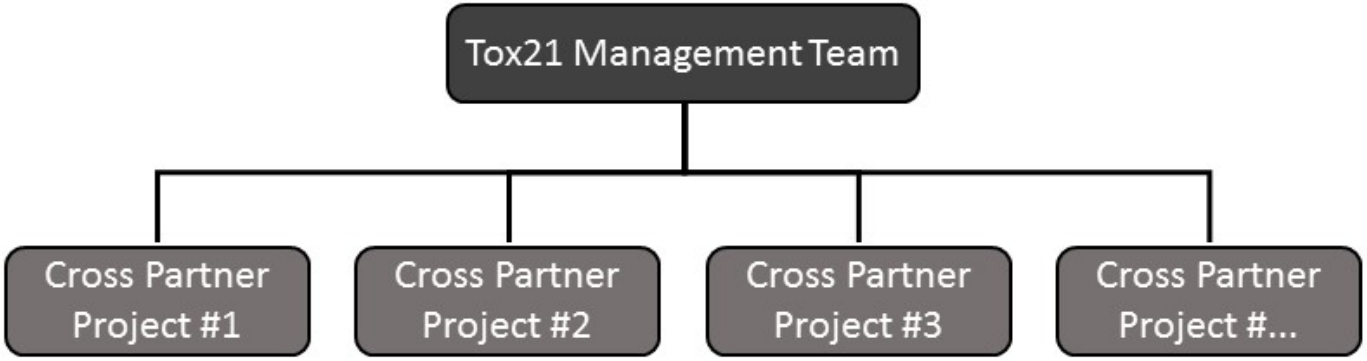
Areas of Focus

1. Develop and deploy alternative test systems that are predictive of human toxicity and dose response
2. Address key technical limitations of current *in vitro* test systems
3. Curate and characterize legacy *in vivo* toxicity studies to serve as a resource for interpreting Tox21 data
4. Develop framework for efficient validation of Tox21 approaches
5. Refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty

New Tox21 Structure



New Tox21 Structure



Cross-Partner Projects

- Project charters
- 3 year terms
- Project leads from two or more partners
- Reviewed annually

Initial Infrastructure Teams and Example Cross Partner Projects

Infrastructure Teams

- Chemical Library Management
- Communications
- Assay Evaluation and Screening

Cross-Partner Projects

- *In Vitro* Disposition of Tox21 Chemicals
- Performance Based Validation of Tox21 Assays
- Development of a Reference Chemical Dataset for Interpretation of High-Throughput Transcriptomic Screening Data
- Incorporating Genetic Susceptibility into Developmental Neurotoxicity Screening
- Development of a High-Throughput Assay to Identify 5-α Reductase Inhibitors for Orthogonal Evaluation in an Androgen-dependent Human 3D Prostate Tissue
- Cell Line Selection for High-Throughput Transcriptomic Screening
- Predictive Modeling of Developmental Toxicity with Human Pluripotent Stem Cells
- Development of a High-Throughput Assay to Identify Acetylcholinesterase Inhibitors

EPA

NTP
National Toxicology Program
U.S. Department of Health and Human Services

Thank You for Your Attention!

FDA

NIH National Center for Advancing Translational Sciences

NIH National Institute of Environmental Health Sciences